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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,768	10/29/2001	Eric H. Baehrecke	4115-131	3246

23448 7590 10/21/2004

INTELLECTUAL PROPERTY / TECHNOLOGY LAW
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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,768	BAEHRECKE, ERIC H.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07/28/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,13,20,21,23,24 and 26-32* is/are pending in the application.

4a) Of the above claim(s) *13,21,23,24 and 29-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,20 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The finality of the previous Office action has been withdrawn, and the prosecution of this application is reopened to include a rejection not previously cited.

It is noted that applicant has paid for a Notice of Appeal. Applicant can either request a refund or place the funds on credit for future appeals.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 3, 22.

Accordingly, claims 1-2, 20, 26-28 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT, NEW REJECTION

Claims 1-2, 20, 26-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-2, 20, 26-28 are drawn to an isolated polyeptide that induce cell death in vitro, consisting of or comprising SEQ ID NO:8, and a variant thereof.

The specification discloses that the polynucleotide encoding SEQ ID NO:8 could induce programmed cell death in vitro, when transfected into human cell lines (Example 2, pages 42-43).

The specification contemplates the use of the polypeptide of SEQ ID NO:8 for treating and preventing cancers, and the use of an antagonist of SEQ ID NO:8 for treating diseases having an increase in cell death, such as AIDS, neurodegenerative diseases, ischemic injuries, toxin-induced diseases, wasting diseases (p.40 under Therapeutics).

The specification contemplates using the claimed polypeptide for screening substances that interact with the claimed polypeptide (p.39, under Screening assays).

One cannot extrapolate the teaching in the specification to the enablement of the claims. Although SEQ ID NO:8 could kill cells in vitro, one cannot predict that SEQ ID NO:8 could be used in vivo for treating or preventing a diseases having an increase or decrease in proliferation, because conditions in vitro and in vivo are not the same, wherein in in vitro conditions, the target cells are continuously exposed to the test substance, and are not subjected to homeostasis, which renders treating diseases cited in the specification unpredictable. For example, Kimmel et al.(J. Neurosurg, 66:161-171, 1987) who teach that in vitro assays cannot easily assess host-tumor and cell-cell interactions that may be important in the malignant state and cannot duplicate the complex conditions of in vivo therapy. Similarly, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their

counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. In addition, Xu Xin et al, 2001, FASEB J, 15(4): A313, teach that compensatory mechanism could regulate apoptosis to overcome the low induction of Fas and FasL in activated CD4+ cells of IRF-1 null mice. Moreover, it is unpredictable that the claimed SEQ ID NO:8 could induce programmed cell death or apoptosis in vivo, because it is well known in the art that there exists several apoptosis antgonists, such as members of the Bcl-2 family and CrmA that act upstream of the effector caspase-3 and-6, e.g. inhibition of the activation of the initiator caspase-9 (Colussi, PA et al, 1998, J Biol Chem, 273(41): 26566-26570, especially p.26569, first column), and that the cellular concentration of members of the apoptosis antagonist Bcl-2 family is directly related to whether a cell will respond to an apoptotic signal; and further, resistance of mature thymocytes to apoptotic signals correlates with high expression level of Bcl-2 protein, and overexpression of a cell death promoter BAD would counter the death inhibitory activity of Bcl-XL (Oltvai et al, 1994, Cell, 79: 189-192). Thus one cannot predict that in *in vivo* conditions, due to homeostasis, an increase in the concentration of the claimed polypeptide of SEQ ID NO:8 would not be countered by an increase in apoptosis-antagonist proteins. Furthermore, Schimmer, AD, 2003, Cancer Res, 63(6):

1242-8 teach that cancer cells such as leukemia could overepxress endogenous inhibitors of the effector caspases, and block the caspase pathways. Thus it is unpredictable that the claimed compound could be useful for treating cancer, due to possible inhibition of caspase activity resulting in inhibition of programmed cell death, or apoptosis, by the overexpression of inhibitors the effector caspases in cancer patients.

Moreover, one cannot extrapolate the teaching of the specification to the enablement of the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed polypeptide could be used for treating cancer. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to

overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed polypeptide could be used for treating cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

In addition, therapeutic agents must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the target cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. Also, the target cell must not have

an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established. For example, Mahoney et al, 1999, Proceed Natl Acad Sci USA, 96(8): 4536-4539, teach that toxicity prevents the systemic administration of many therapeutic proteins, and attempts at protein targeting via the circulatory system has failed in all but a few special cases. Mahoney et al further teach that for treating Alzheimer's disease, proper local delivery is essential, and that efficacy of treatment is correlated with the spatial distribution of nerve growth factor concentration in the tissue, wherein nerve growth factor must be delivered within 1-2 mm of the target to be effective in treating Alzheimer's disease. The specification, however, does not disclose how to target the claimed agent to the site of the diseases cited in the specification, including the neurological diseases. For example, the specification does not disclose which specific neuronal populations of Alzheimer's disease are responsive to SEQ ID NO:8, and how to target the claimed agent to the sites of said populations of the neurological disease. Further, regeneration of the already damaged neurons in these neurodegenerative

disease states are required, because without functional synaptogenesis, there is no functional regeneration. However, it is well known in the art that neurons do not regerenate in the CNS (Jackowski et al, 1995, British J Neurosurgery, 1995, 9: 303-317, especially p.305, p.09-310). The specification fails to provide any guidance on how to treat any of the unique disorders associated with increased or decreased cell deathl, as cited in the specification, each with their unique etiology, and unique responses to drugs, especially in view that treatment of these disorders is unpredictable, for reasons set forth above.

In addition, since one does not know how to use the claimed polypeptide, one would not know how to use the screened substances that interact with the claimed polypeptide.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

If Applicant could overcome the above 112, first paragraph, claims 20, 28 remain rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for variants of SEQ ID NO:8, for reasons already of record in paper of 05/28/04.

Applicant asserts that the claims were amended to have the following four parameters:

1) At least 90% homology to SEQ ID NO:2.

2) A conserved carboxy-end region having an amino acid sequence of amino acid residues of 39-53 of SEQ ID NO:2,

3) Conservative changes in any amino acid substitutions, and

4) induces cell death in vitro.

Applicant argues that substitution is limited to replacement and does not include deletion or additional amino acid residues, and that conservative substitutions would not change the biological functionality. Applicant argues that the specification provides guidance on how to make and use the claimed functional variants.

Applicant asserts that Lazar et al teach conservative substitution, wherein said substitution provides functional activity, albeit at reduced activity. Applicant argues that the substitution in Burgess et al is not conservative, and thus a drastic reduction in activity of HBGF-1 is not surprising. Applicant argues that Bowie et al support the importance of conservative substitution, when reciting that in certain positions, no substitution or only conservative substitution are allowed.

Applicant argues that since there is correlation and interconnection between written description and enablement requirement, and since there is no written description rejection in the instant application, the claims inherently meet the enablement requirements.

Applicant's arguments set forth in paper of 07/28/04 have been considered but are not deemed to be persuasive for the following reasons:

Contrary to Applicant's arguments, the claims are not limited to variants that only have conservative substitutions, but encompass variants having deletion and/or addition

at any amino acid position, wherein the added amino acids could be any amino acids, provided that the substitution, addition and/or deletion does not exceed 5% difference to SEQ ID NO:8. The specification does not provide guidance on which amino acid to be added or deleted such that the claimed variants still retain the cell death activity.

Further, although some conservative substitutions at certain positions of a sequence could retain some of the original activity of the sequence, not any conservative substitution at any amino acid position would retain some of the original activity of the sequence. For example, Straub P et al, 1993, J Biol Chem 268(29): 21997-20003, teach that conservative substitutions of valine for glycine at positions 111 and 117 of cytochrome P450 2C2 result in about 50- and 7-fold reduction of activity, respectively. Kouklis PD et al, 1993, J Cell Science, 106(pt 3): 919-28, teach that a single exchange of glycine 450 of the intermediate filament protein vimentin with valine strongly interfers with the normal assembly of the intermediate filaments. Assemat, K et al, 1995 (Protein Science, 4 : 2510-2516, especially p.2510, first column, first paragraph, page 2513, second column, two paragraphs before last paragraph) teach that conservative substitution in the hydrophobic core can effect different biological function in different ways, and that intimate packing of hydrophobic side chain at internal positions is important for protein folding and stability, wherein subtle disruptions of the packed protein core can result in dramatic effects on both stability and function. Thus, although conservative substitutions increase the chance of having less effect on the activity of the protein, it is unpredictable which amino acid at a certain position could be substituted even by conservative substitution.

In addition, it is noted that Bowie et al also teach that in certain positions, no substitutions are allowed, and thus indicating although some conservative substitutions are allowed, in some positions no substitutions are allowed.

Moreover, although the claims meet the written description, the claims do not meet the enablement requirement, because one does not know how to make and use the claimed variants, which is strictly an enablement issue, and not a written description issue.

REJOINING THE METHOD CLAIMS

Applicant requests that all the method and use claims that are currently withdrawn be rejoined, and taken up for examination.

It is noted that *In re Ochiai*, 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995) and *In re Brouwer*, 77 F.3d 422, 37 USPQ2d 1663 (Fed. Cir. 1996) addressed the issue of whether an otherwise conventional process could be patented if it were limited to making or using a nonobvious product, only when the product claim is found allowable.

"In situations where product and process claims drawn to independent and distinct inventions are presented in the same application, an applicant may be called upon under 35 U.S.C. §121 to elect claims to either the product or process. The claims to the non-elected invention will be withdrawn from further consideration. However, in the case of an elected product claim, when a product claim is found allowable, withdrawn process claims which depend from or otherwise include all the limitations of an allowable product claim will be rejoined."

Thus, since the claimed products are presently not found allowable, the issue of rejoining method claims should be delayed until allowance time, if the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS

October 13, 2004

SUSAN UNGAR, PH.D
PRIMARY EXAMINER